Tetrahedron Letters,Vol.29,No.17,pp 2069-2072,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A STEREOSPECIFIC SYNTHESIS OF (4R)-4-[(E)-2-BUTENYL]-4,N-DIMETHYL-L-THREONINE (MeBmt)

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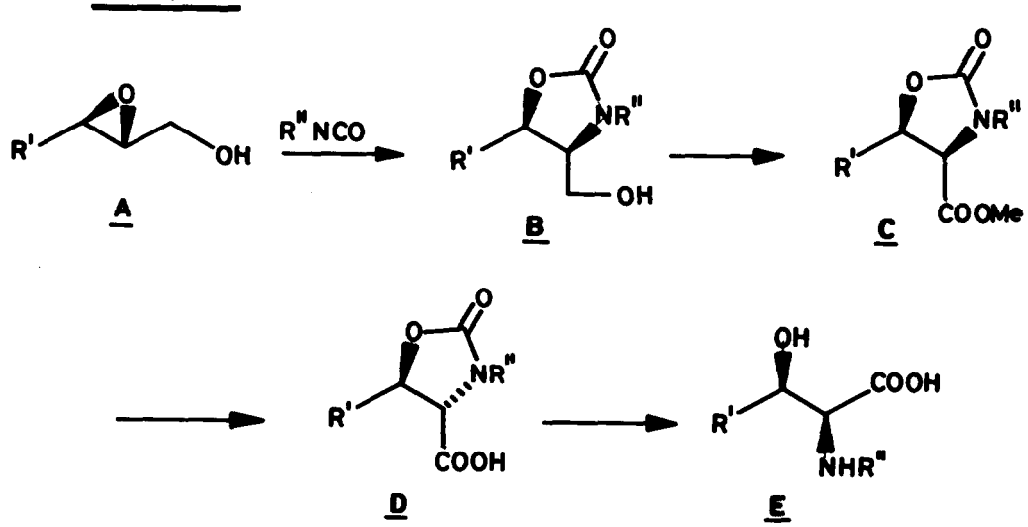
Abstract *The utility of readily obtainable cis-oxazolidinone derivative (14) has been explored for the efficient and stereospecific synthesis of (4R)-4-[(E)-2-butenyl]-4,N-dimethyl-L-threonine, an unusual syn-β-hydroxy-α-amino acid of cyclosporine.*

Unusual β-hydroxy-α-amino acids are frequently encountered as part structures of many biologically active peptides[1,2]. During our studies on MeBmt (1)[3], an unusual amino acid of cyclosporine (2), we felt the need to develop a simple, efficient and complementary protocol to construct β-hydroxy-α-amino acid framework. The ready availability[4] of oxazolidinone derivatives B (Scheme 1), in optically active forms from corresponding 2,3-epoxy-alcohols (A) was realised as particularly useful intermediates

Scheme - 1



for achieving the desired goal. Subsequent oxidation of the hydroxymethylene group in (B) followed by epimerization (D)[5] and hydrolysis[6] would lead to the syn-β-hydroxy-α-amino acid substitution pattern (E) as required in MeBmt. This report deals with an application of this approach for the stereospecific synthesis of MeBmt.

Our first concern was the synthesis of the allylic alcohol (10), a useful precursor for chiral 2,3-epoxyalcohol. Thus, alkylation of ethyl 2-carbethoxypropionate with E-crotyl bromide (NaOEt,

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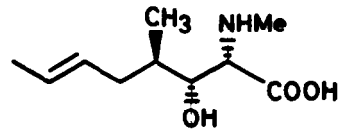
RRL communication no. 2104

EtOH, RT) was followed by decarboxylative saponification (ethanolic KOH followed by distillation of the diacid) to afford the acid (3). For effecting the resolution[7] of the (±) acid (3), the derived acid chloride (4) ($SOCl_2$,RT) and phenylalanilol were condensed (Et_3N, dioxane,RT) to give a chromatographically separable diastereomeric mixture of amides (5 and 6). The required amide (6) was hydrolysed (3N H_2SO_4, dioxane-water) and then reduced (LAH, THF,Δ) to afford the alcohol (7) whose physical and spectral properties were identical with the authentic data[3b]. Swern oxidation ($DMSO,(COCl)_2,Et_3N$, -78°C, 3h) of 7 afforded a rather unstable aldehyde (8). Subsequent Wittig reaction (Ph_3P=CHCOOEt,



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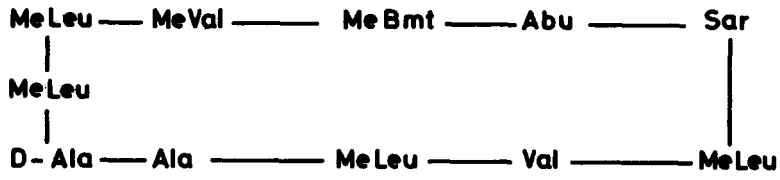

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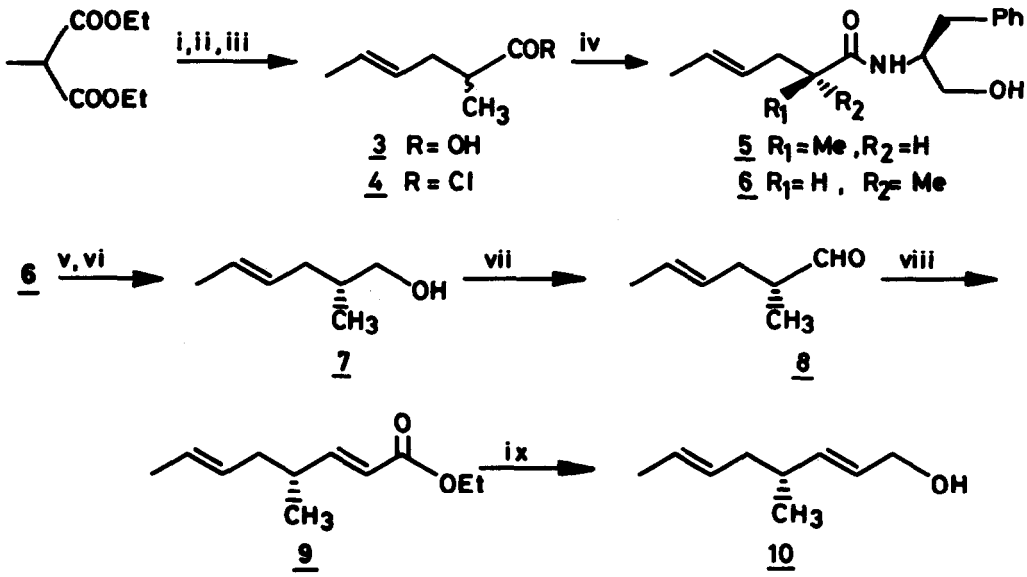
Scheme - 2

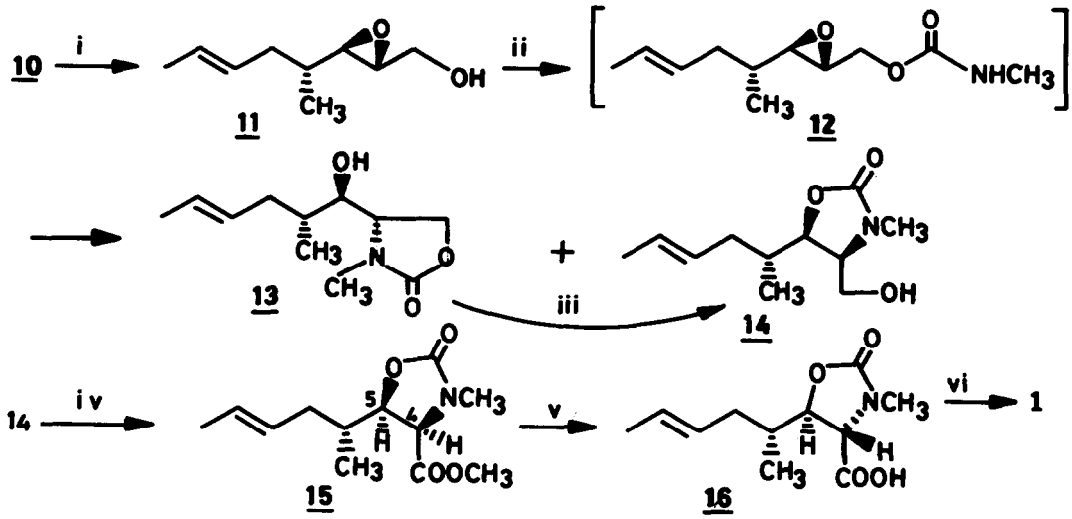


i. $NaOC_2H_5$ (1.1 eq), 0°C to RT, 1 h, (E)-crotyl bromide (1 eq); ii. KOH, abs. EtOH; followed by heating; iii. $SOCl_2$ (1.2 eq), C_6H_6, 0°C to RT, 12 h; iv. L-phenylalaninol (1 eq), Et_3N (1.5 eq), dioxane, RT, 1 h; v. 3N H_2SO_4, dioxane-H_2O (1:1), reflux, 3 h; vi. LAH (1.1 eq), THF, reflux, 1 h; vii. $(COCl)_2$ (1.4 eq), DMSO (2.8 eq), Et_3N (4.4 eq), CH_2Cl_2, -78°C to -20°C, 3 h; viii. C_6H_6, RT, Ph_3P=$CHCO_2Et$ (1 eq), 2 h; ix. DIBAL-H (2.5 eq), CH_2Cl_2), -78°C, 0.5 h.

C_6H_6, RT) of **8** afforded exclusively the trans-α,β-unsaturated ester (**9**) (70%). The reduction of the carboxylate group in **9**[8] was effected with DIBAL-H (-78°C, CH_2Cl_2) to give the allylic alcohol (**10**) (90%) (Scheme 2).

Sharpless epoxidation[9] [(-)DIPT, TBHP, TTIP] of **10** gave the 2,3-epoxy alcohol derivative (**11**) (82%). The stereochemical assignment of **11** was assigned by taking into account the predictions reported by Sharpless (Scheme 3). Treatment of **11** with methylisocyanate in the presence of sodium

Scheme - 3



i. $Ti(OPr)_4$ (1 eq), (-) DIPT (1 eq), TBHP (2 eq), CH_2Cl_2, -25°C, 16 h; ii. NaH (2.15 eq), MeNCO (1.5 eq), THF, reflux, 2 h; iii. NaH (0.5 eq), THF, RT, 1 h; iv. a) Jones oxidation, b) CH_2N_2, Et_2O, RT, 30 min; v. 0.89 N KOH (1.01 eq), EtOH, reflux, 30 min; vi. 2N KOH (aq), 5 h, reflux.

hydride (refluxing THF) first formed the urethane intermediate (**12**) which in situ underwent rearrangement[4] to afford a chromatographically separable 3:2 mixture of isomeric oxazolidinone derivatives (**13** and **14**) (75% overall yield). The undesired isomer **13** was partially rearranged (NaH, THF, RT) and a further 1:1 mixture of **13** and **14** were obtained. The combined isolated derivative **14** (37%) was subjected to Jones oxidation (Jones reagent, acetone, RT) and consequently esterified (CH_2N_2, ether, RT) to give the allothreonine product (**15**) having cis-oxazolidinone ring (75%).

Compound **15** had all the stereochemical centers in conjunction with MeBmt except for the the carbon atom 4 whose chirality has to be inverted. Thus, treatment of **15** with refluxing ethanolic KOH afforded the more stable trans product **16**[5] (80%). The structure of **16** was proved without doubt by the comparison of its ^1H NMR spectrum with that of the parent compound **15**. Whilst, the resonance due to H-4 were apparent in both the spectra as a doublet, the small observed value for $J_{4,5}$ (4.8 Hz) for **16** (as compared to 10.8 Hz for **15**) was in complete agreement with trans configuration. Moreover the $[\alpha]_D$ value for **16** was in agreement with the literature value {$[\alpha]_D$ + 30.5° (c 0.26, $CHCl_3$), Lit.[3a] $[\alpha]_D$ + 33.5° (c 1, $CHCl_3$)}. Finally, the deprotection of the oxazolidinone ring in **16** was carried out in the presence of an alkali, (2N KOH reflux) in accordance with the literature procedure[3a] to

give **1**, identical in all respects with the reported sample.

References and notes

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(Received in UK 4 March 1988)